

RECEIVED  
CENTRAL FAX CENTER

DEC 29 2006 DOCKET NO: ISIS-5027

APPLICANT: Stanley T. Crooke  
SERIAL NO: 10/078,949

#### REMARKS

Claims 165-201 were pending. Upon entry of this Amendment, claims 165, 167-183 and 202-257 will be pending. Claims 166 and 184-201 are canceled herein without prejudice to their presentation in another application. Claims 165 and 167 are amended and new claims 202-257 are submitted herein. Claim 165 is amended to: insert a second method step of detecting activation of the double-stranded RNA nuclease; replace "modified nucleoside" with "chemical modification" for clarity and to provide proper antecedent basis for claims depending therefrom; and correct minor grammatical errors. Claim 167 is amended to replace "modified nucleoside or nucleosides" with "chemical modifications" for proper antecedent basis. New claims 202-257 find basis in the claims and specification as originally filed. For example, support for the length limitations of 15 to 25, or 17 to 20, nucleoside subunits can be found on pages 24 and 93 of the specification. Support for the chemical modifications described in claims 203-211, 220-228, 237-254 and 248-256 can be found in the original claims and on pages 7-11 and 22-25 of the specification. Basis for claims 215 and 232 can be found, for example, in Table 1 on page 93 of the specification. Table 1 shows an example of a double-stranded RNA with 17 contiguous nucleotides which are 100% complementary to each other. Support for oligonucleotides comprising "a plurality of nucleoside subunits with 2'-hydroxyl pentofuranosyl sugar moieties" can be found, for example, on pages 12 and 13 of the specification and in the original claims. No new matter has been added to the claims.

The specification is amended to correct inadvertent typographical and spelling errors. The amendment to Table 1 correctly identifies each oligonucleotide as having a 5' end and a 3' end. No new matter has been added to the specification.

The claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action. Applicant reserves the right to file subsequent applications claiming the canceled subject matter.

#### REJECTIONS UNDER 35 U.S.C. §102(e)

Claims 184-186, 190, 191 and 197-199 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Goodchild *et al.* (U.S. 6,573,072).

Claims 184-186, 190, 191 and 197-199 have been canceled, rendering the rejection moot as it pertains to these claims. Furthermore, Goodchild *et al.* do not anticipate new claims 202-257. Goodchild *et al.* do not teach or even suggest (i) a double-stranded RNA in

APPLICANT: Stanley T. Crooke  
SERIAL NO: 10/078,949

DOCKET NO: ISIS-5027

which both strands are 15 to 25 nucleotides in length; (ii) a double-stranded RNA in which the oligonucleotides are 100% complementary to each other; and/or (iii) a double-stranded RNA in which both strands comprise at least one chemical modification. Thus, Goodchild *et al.* do not anticipate new claims 202-257.

Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §102(e).

Claims 165-167, 172, 173, 179, 180, 184, 185, 190, 191, 197 and 198 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Usman *et al.* (U.S. 6,849,726). The Office Action asserts Usman *et al.* disclose modified ribozymes which are introduced into a cell for hybridization and cleavage of a substrate RNA. The Office Action concludes Usman *et al.* meets all the limitations of the rejected claims since the double stranded RNA was brought into contact with an RNA nuclease by virtue of being administered to a cell. Applicant respectfully traverses this rejection.

Claims 184, 185, 190, 191, 197 and 198 have been canceled, rendering the rejection moot as it pertains to these claims. As amended herein, claims 165-167, 172, 173, 179, 180 require two method steps: (i) contacting a nuclease with a double-stranded RNA comprising the features listed in claim 165; and (ii) detecting activation of the double-stranded RNA nuclease.

In order to anticipate a claim, the prior art must teach each and every limitation of the claim. Usman *et al.* teach modified ribozymes hybridized to a substrate RNA. The ribozymes taught by Usman *et al.* and ribozymes well known to those of ordinary skill in the art, are designed to cleave the substrate RNA to which they hybridize. Usman *et al.* do not teach any double-stranded RNA nucleases let alone teach or suggest detecting activation of a double-stranded RNA nuclease. Therefore, Usman *et al.* do not anticipate the rejected claims.

Usman *et al.* also do not anticipate new claims 202-257. Usman *et al.* do not teach or even suggest (i) a double-stranded RNA in which both strands are 15 to 25 nucleotides in length; (ii) a double-stranded RNA in which the oligonucleotides are 100% complementary to each other; or (iii) a double-stranded RNA in which both strands comprise at least one chemical modification. Thus, Usman *et al.* does not anticipate new claims 202-257.

Since Usman *et al.* do not teach each and every element recited in the instant claims, the pending claims are not anticipated. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §102(e).

APPLICANT: Stanley T. Crooke  
SERIAL NO: 10/078,949

DOCKET NO: ISIS-5027

#### REJECTIONS UNDER 35 U.S.C. §103(a)

Claims 189, 192 and 193 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Goodchild *et al.* (U.S. 6,573,072).

Claims 189, 192 and 193 have been canceled, rendering the rejection moot. Furthermore, Goodchild *et al.* do not render obvious new claims 202-257. Goodchild *et al.* do not teach or even suggest (i) a double-stranded RNA in which both strands are 15 to 25 nucleotides in length; (ii) a double-stranded RNA in which the oligonucleotides are 100% complementary to each other; and/or (iii) a double-stranded RNA in which both strands comprise at least one chemical modification. Thus, new claims 202-257 are not obvious in view of Goodchild *et al.*

Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103(a).

Claims 187 and 188 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Goodchild *et al.* in view of Uhlmann *et al.* (U.S. 6,037,463).

Claims 187 and 188 have been canceled, rendering the rejection moot. Furthermore, the combination of Goodchild *et al.* and Uhlmann *et al.* do not render obvious new claims 202-257. Neither Goodchild *et al.* nor Uhlmann *et al.*, alone or in combination, teach or even suggest (i) a double-stranded RNA in which both strands are 15 to 25 nucleotides in length; (ii) a double-stranded RNA in which the oligonucleotides are 100% complementary to each other; and/or (iii) a double-stranded RNA in which both strands comprise at least one chemical modification. Thus, new claims 202-257 are not obvious over Goodchild *et al.* in view of Uhlmann *et al.*

Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103(a).

Claims 165-169, 171-173, 175, 179, 180, 184-187, 189-191, 193, 197 and 198 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Usman *et al.* (U.S. 6,849,726). The Office Action asserts Usman *et al.* teach modified ribozymes hybridized to a target RNA, which in a cell, would be contacted by a double stranded RNA nuclease. The Office Action concludes that Usman *et al.* meet all of the structural limitations of the claims and since the claimed method requires only one step of contacting a double stranded RNA

APPLICANT: Stanley T. Crooke  
SERIAL NO: 10/078,949

DOCKET NO: ISIS-5027

nuclease with a double stranded RNA, the claims are obvious. Applicant respectfully traverses this rejection.

Claims 184-187, 189-191, 193, 197 and 198 have been canceled, rendering the rejection moot as it pertains to these claims. Claims 165-169, 171-173, 175, 179 and 180, as amended, are directed to a method of activating a double-stranded RNA nuclease, wherein the method requires two steps: (i) contacting a nuclease with a double-stranded RNA comprising the features listed in claim 165; and (ii) detecting activation of the double-stranded RNA nuclease.

In order to establish a *prima facie* case of obviousness, the prior art must, *inter alia*, teach or suggest each and every limitation of the claims. As discussed above in reference to the rejection under 35 U.S.C. § 102(e), Usman *et al.* do not teach, or even suggest, the second method step of detecting activation of the double-stranded RNA nuclease.

Furthermore, Usman *et al.* do not render obvious new claims 202-257. Usman *et al.* do not teach or even suggest (i) a double-stranded RNA in which both strands are 15 to 25 nucleotides in length; (ii) a double-stranded RNA in which the oligonucleotides are 100% complementary to each other; and/or (iii) a double-stranded RNA in which both strands comprise at least one chemical modification. Thus, new claims 202-257 are not obvious in view of Usman *et al.*

Applicant respectfully submits Usman *et al.* do not teach or even suggest each and every limitation of the pending claims, thus the Office has failed to establish a *prima facie* case of obviousness. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103.

Claims 170 and 188 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Usman *et al.* in view of Uhlmann *et al.* The asserted teachings of Usman *et al.* are described above. The Office action states Usman *et al.* do not specifically teach a 2'-O-methoxyethyl modification; however, Uhlmann *et al.* teach that such 2' modifications are known and routinely used in the art. Thus, the Office Action concludes it would have been obvious to modify the double stranded RNA of Usman *et al.* with the 2'-O-methoxyethyl modification taught by Uhlmann *et al.* Applicant respectfully traverses this rejection.

Claim 188 has been canceled, rendering the rejection moot as it pertains to this claim. Claim 170 depends indirectly from claim 165, the limitations of which are described above, and further requires that at least one oligonucleotide modification is a 2'-O-methoxyethyl.

APPLICANT: Stanley T. Crooke  
SERIAL NO: 10/078,949

DOCKET NO: ISIS-5027

In order to establish a *prima facie* case of obviousness, the prior art must, *inter alia*, teach or suggest each and every limitation of the claims. As discussed above in reference to the rejections under 35 U.S.C. §102(e) and §103(a), Usman *et al.* do not teach, or even suggest, the second method step of detecting activation of the double-stranded RNA nuclease. The Uhlmann *et al.* reference, which also teaches RNA ribozymes, does not cure the deficiencies of Usman *et al.*

Furthermore, the combination of Usman *et al.* and Uhlmann *et al.* do not render obvious new claims 202-257. Neither Usman *et al.* nor Uhlmann *et al.*, alone or in combination, teach or even suggest (i) a double-stranded RNA in which both strands are 15 to 25 nucleotides in length; (ii) a double-stranded RNA in which the oligonucleotides are 100% complementary to each other; and/or (iii) a double-stranded RNA in which both strands comprise at least one chemical modification. Thus, new claims 202-257 are not obvious over Usman *et al.* in view of Uhlmann *et al.*

Applicant respectfully submits Usman *et al.* and Uhlmann *et al.*, alone or in combination, do not teach or even suggest each and every limitation of the pending claims, thus the Office has failed to establish a *prima facie* case of obviousness. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103.

#### CLAIM OBJECTIONS

Claims 174, 176-178, 181-183, 194-196, 200 and 201 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form. Claims 194-196, 200 and 201 have been canceled, rendering the objection against these claims moot. Applicant respectfully submits that the remaining objected claims depend from claims that are in condition for allowance. Thus, Applicant respectfully requests withdrawal of the claim objections.

It is believed that no fee is due with this response. However, if a fee is due, the Commissioner is hereby entitled to charge the fee to Deposit Account 50-0252, referencing the above named application.

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record and the subsequent notice of Non-Responsive Amendment. Withdrawal of the pending rejections and reconsideration of the claims is respectfully requested. If the Examiner believes that there are any remaining issues in the case that could

APPLICANT: Stanley T. Crooke  
SERIAL NO: 10/078,949

DOCKET NO: ISIS-5027

be resolved by a telephonic interview, the Examiner is encouraged to contact the Agent for Applicant listed below to discuss any outstanding matters.

Respectfully submitted,



Jodi L. Connolly, Ph.D.  
Registration No. 54,044

Date: 12/29/2006

ISIS Pharmaceuticals, Inc.  
1896 Rutherford Rd.  
Carlsbad, CA 92008  
Telephone: (760) 603-2777  
Facsimile: (760) 603-3820